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Arrhythmogenic Right Ventricular Cardiomyopathy

Clinical Course and Predictors of Arrhythmic Risk

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ABSTRACT

BACKGROUND Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a leading cause of sudden cardiac death, but its progression over time and predictors of arrhythmias are still being defined.

OBJECTIVES This study sought to describe the clinical course of ARVC and occurrence of life-threatening arrhythmic events (LAE) and cardiovascular mortality; identify risk factors associated with increased LAE risk; and define the response to therapy.

METHODS We determined the clinical course of 301 consecutive patients with ARVC using the Kaplan-Meier method adjusted to avoid the bias of delayed entry. Predictors of LAE over 5.8 years of follow-up were determined with Cox multivariable analysis. Treatment efficacy was assessed comparing LAE rates during matched time intervals.

RESULTS A first LAE occurred in 1.5 per 100 person-years between birth and age 20 years, in 4.0 per 100 person-years between ages 21 and 40 years, and in 2.4 per 100 person-years between ages 41 and 60 years. Cumulative probability of a first LAE at follow-up was 14% at 5 years, 23% at 10 years, and 30% at 15 years. Higher risk of LAE was predicted by atrial fibrillation (hazard ratio [HR]: 4.38; $p = 0.002$), syncope (HR: 3.36; $p < 0.001$), participation in strenuous exercise after the diagnosis (HR: 2.98; $p = 0.028$), hemodynamically tolerated sustained monomorphic ventricular tachycardia (HR: 2.19; $p = 0.023$), and male sex (HR: 2.49; $p = 0.012$). No difference was observed in the occurrence of LAE before and after treatment with amiodarone, beta-blockers, sotalol, or ablation. A total of 81 patients received an implantable cardioverter-defibrillator, 34 were successfully defibrillated.

CONCLUSIONS The high risk of life-threatening arrhythmias in patients with ARVC spans from adolescence to advanced age, reaching its peak between ages 21 and 40 years. Atrial fibrillation, syncope, participation in strenuous exercise after the diagnosis of ARVC, hemodynamically tolerated sustained monomorphic ventricular tachycardia, and male sex predicted lethal arrhythmias at follow-up. The lack of efficacy of antiarrhythmic therapy and the life-saving role of the implantable cardioverter-defibrillator highlight the importance of risk stratification for patient management. (J Am Coll Cardiol 2016;68:2540–50) © 2016 by the American College of Cardiology Foundation.

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited disease (1) characterized by progressive replacement of the myocardium by adipose and fibrous tissue (2) that predisposes to development of ventricular tachycardia (VT) and to sudden cardiac death (SCD). This condition was described 3 decades ago, when fibrofatty infiltration in the right ventricle was considered its pivotal indicator (3,4). It later became clear that ARVC is mainly caused by mutations in the genes encoding for desmosomal proteins (1). This helped establish that the disorder is often associated with biventricular manifestations (5), and the term *arrhythmogenic cardiomyopathy* has also been proposed (1). The unmet need in managing patients with ARVC is represented by the lack of an evidence-based scheme to identify individuals who are at high risk of SCD.

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Here we present data on the clinical course of patients with ARVC from our registry, highlighting the importance of behavioral risk factors in disease progression, and providing information that may affect clinical management. In describing the clinical manifestations of ARVC in our cohort, we adopted a different statistical approach from the one used by previous studies: we took into account the survivorship bias inherent in studying populations who are not followed-up since birth (6), which might have generated overly optimistic conceptions about ARVC severity.

We also report data on the risk predictors for the first life-threatening arrhythmia occurring during a median observation time of 5.8 years, and describe the effect of antiarrhythmic drugs, transcatheter ablation, and implantable cardioverter-defibrillators (ICDs) on the prognosis of patients with ARVC.

METHODS

A list of the definitions used (Online Table 1) and a detailed description of the clinical assessment and management of patients and of the genetic screening performed are in the Online Appendix.

AIMS AND ENDPOINTS. There were 3 aims to our study. First, we sought to describe the clinical course of ARVC, assessing the occurrence of a first life-threatening arrhythmic event (LAE) defined as SCD, aborted cardiac arrest, syncopal VT or electrical storm, or cardiovascular mortality. At variance with prior studies that examined predictors of any sustained ventricular arrhythmia or "malignant" ventricular arrhythmias (cycle length <240 ms), we selected a novel endpoint.

Second, we evaluated the occurrence of LAE at follow-up and sought to identify predictors of the first LAE.

Finally, we worked to define the response to therapy at follow-up.

STATISTICAL ANALYSIS. Statistical analysis was performed using SPSS version 21 (IBM Corporation, Armonk, New York) and R version 3.0 (R Foundation, Vienna, Austria). Data are expressed as percentage, mean ± SD, or median with interquartile range (IQR) for skewed distributions.

Previous studies have described the "natural history" of ARVC by applying the Kaplan-Meier analysis to the time interval between birth and last follow-up (7,8). This approach, albeit widely used, is methodologically flawed as it overestimates survival probability. Patients diagnosed with ARVC at older ages, by virtue of having survived to the time of diagnosis, could not have had an event between birth and the time of diagnosis. This phenomenon, called delayed entry or left-truncation, is common in studies where the time variable of interest is the age of an individual. To avoid this bias, we removed patients from the risk set between birth and diagnosis of ARVC, and considered only the time during which patients were followed prospectively. For this reason, 15 patients who experienced SCD as the first manifestation of ARVC and 8 patients lost to follow-up were not included in the analysis. The survival function was estimated using the adjusted Kaplan-Meier estimator proposed by Tsai et al. (6). Considering that the youngest patient included in the analysis was 1.9 years of age at the beginning of observation and that the probability of experiencing an LAE related to ARVC in early infancy is deemed to be extremely low (9,10), we described the clinical manifestations of our cohort from birth.

To highlight the behavior of ARVC in different age groups, we reported incidence rates for LAE and for cardiovascular mortality according to the following categories: from birth to age 20 years, from age 21 to 40 years, and from age 41 to 60 years.

Incidence rates were computed by dividing the number of patients experiencing a first LAE or cardiovascular death by the total number of person-years. Also, to adjust for delayed entries, the time from birth to diagnosis was not considered in the person-years calculation.

During follow-up, we recorded LAE occurrence both in patients who presented for medical attention after surviving an LAE with documented ventricular fibrillation (VF) (n = 11) and in those

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ARVC = arrhythmogenic right ventricular cardiomyopathy

HT-MMVT = hemodynamically tolerated sustained monomorphic ventricular tachycardia

ICD = implantable cardioverter-defibrillator

IQR = interquartile range

LAE = life-threatening arrhythmic event

SCD = sudden cardiac death

VF = ventricular fibrillation

VT = ventricular tachycardia